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(71) Applicants: **SPECTRAL DIMENSIONS, INC.** [US/US]; Suite 102, 3403 Olandwood Court, Olney, MD 20832 (US). **THE GOVERNMENT OF THE UNITED STATES OF AMERICA, represented by THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES** [US/US]; Suite 325 6011 Executive Boulevard Rockville, MD 20852-3804 (US).

(72) Inventors: **LEWIS, Neil, E.**; 2440 Saint Albert Terrace, Brookville, MD 20833 (US). **STRACHAN, David, J.**; 12 Wood Raven Court, Baltimore, MD 21234 (US). **KIDDER, Linda, H.**; 18003 Golden Spring Court, Wolney, MD 20832 (US).

(74) Agent: **ELBING, Kristofer, E.**; 187 Pelham Island Road, Wayland, MA 01778 (US).

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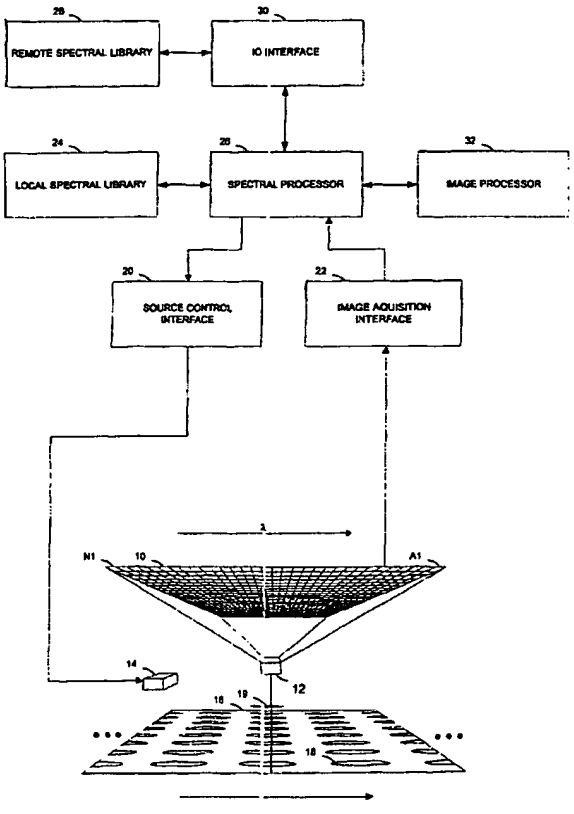
(54) Title: HIGH-VOLUME ON-LINE SPECTROSCOPIC COMPOSITION TESTING OF PHARMACEUTICAL DOSAGE UNITS



(57) Abstract: A pharmaceutical dosage unit manufacturing process control apparatus. This apparatus includes an image sensor (10) including an array of detector elements located generally along an axis that is perpendicular to a direction of flow of pharmaceutical dosage units (18), a spectrally selective element (12) located in an optical path between a radiation source, the flow of pharmaceutical dosage units, and the image sensor. A spectral processor is responsive to an output of the array sensor (26).

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HIGH-VOLUME ON-LINE SPECTROSCOPIC COMPOSITION TESTING OF PHARMACEUTICAL DOSAGE UNITS

Field of the Invention

This invention pertains to quality control systems and methods that detect process defects in large-scale manufacturing processes, such as the manufacture of pharmaceutical dosage units, using continuous spectral imaging techniques.

Background of the Invention

Defects in pharmaceutical products can be highly dangerous, or even fatal. And even if such defects are relatively minor, such as non-uniformly sized capsules, they can result in a significant loss of goodwill by the manufacturer. It is therefore of the utmost importance to avoid such defects.

Several approaches now exist to screen pharmaceutical agents packaged in predetermined dosage units, such as capsules or tablets. These include off-line and on-line methods. Off-line methods include the testing of samples of reagents and end-products using various analytical methods. On-line methods attempt to monitor the process of manufacturing the product to detect defects as they occur.

A number of on-line screening approaches currently exist. One approach includes adding coloring agents to bulk ingredients and optically checking the shape, integrity, and color of the final product. Systems employing this approach can take a series of video images of dosage units and use image processing methods to assess the shape and color of the dosage units. Other systems employ groups of discrete optical detectors to detect different colors and infrared detectors to detect the scattering caused by structural defects. These systems can be complicated to install and maintain, and cannot guarantee a defect-free product.

Summary of the Invention

Several aspects of the invention are presented in this application. These relate to improvements to process control apparatus and methods, including apparatus and methods that detect process defects in large-scale manufacturing processes, such as the manufacture of pharmaceutical dosage units, using continuous spectral imaging techniques.

In one general aspect, the invention features a pharmaceutical dosage unit manufacturing process control apparatus. This apparatus comprises an image sensor including an array of detector elements located generally along an axis that is perpendicular to a direction of a flow of

pharmaceutical dosage units. A spectrally selective element is located in an optical path between a radiation source, the flow of pharmaceutical dosage units, and the image sensor. A spectral processor is responsive to an output of the image sensor and having an output port.

In preferred embodiments, the spectral processor can include a color mapping module operative to map spectral information into a color image including differently colored areas that correspond to different parts of the flow of pharmaceutical dosage units having differing responses to different wavelengths. An additional processor can be operative to evaluate the differently colored areas, with the additional processor having an input responsive to the mapping module and an output for providing information about the areas. The mapping module can be operative to shift a plurality of the wavelengths in a similar manner. The spectral processor can include a spectral comparison module operative to compare spectral signatures from a library of known spectral signatures with spectral information acquired from the image sensor. The spectral comparison module can be operative to perform spectral comparisons between the spectral information acquired from the image sensor and spectral signatures for known ingredients in a pharmaceutical composition of the dosage units. The processor can be operative to receive, identify, and store newly detected spectral signatures reported by the spectral comparison module. The library of known spectral signatures can include a plurality of spectral signatures for known defects. The processor can be operative to receive, identify, and store spectral signatures for newly detected defects reported by the spectral comparison module. The spectral processor can include a spectral comparison module operative to compare spectral information received by the image sensor from a reference sample located proximate the flow of pharmaceutical dosage units with spectral information received by the image sensor from the flow of pharmaceutical dosage units. The image sensor can be a two-dimensional array sensor that further includes detectors located generally along an axis that is parallel to the direction of the flow of pharmaceutical dosage units. The spectrally selective element can include a diffraction grating. The spectral processor can include a color mapping module operative to map spectral information into a color image including differently colored areas that correspond to different parts of the flow of pharmaceutical dosage units having differing responses to different wavelengths. An image processor can be responsive to the output port of the spectral processor and operative to evaluate information from the spectral processor. The image sensor can be an infrared image sensor. The image sensor can be a near infrared image sensor. The radiation source can be directed at the flow of pharmaceutical dosage units at a position to which the image sensor is responsive. The flow of pharmaceutical dosage units can include a series of dosage units located in rows generally perpendicular to the direction of the flow of

pharmaceutical dosage units, with the image sensor including, for each of the dosage units in a row, a plurality of detectors along the axis that is perpendicular to the direction of the flow of pharmaceutical dosage units. The spectral processor can be a real-time processor operative to process the images at a rate that is at least equal to a rate at which images are acquired by the image sensor. The spectral processor can be operative to sequentially process spectral data for each line image acquired by the image sensor. The spectral processor can be operative to receive image data from the image sensor at a rate that is independent of a rate of advance of the flow of pharmaceutical dosage units. The spectral processor can be operative to receive image data from the image sensor at a rate that is independent of a rate of advance of the flow of pharmaceutical dosage units. The spectral processor can be operative to perform univariate spectral manipulations on a spectral data set acquired from the image sensor. The spectral processor can be operative to perform multivariate spectral manipulations on a spectral data set acquired from the image sensor. The spectrally selective element can be a filter having filter characteristics that vary along the direction of flow of pharmaceutical dosage units. The spectrally selective element can be a continuously gradeable filter. The spectrally selective element can include a system that simultaneously projects a plurality of spectrally-discrete versions of a same image onto the image sensor.

In another general aspect, the invention features a pharmaceutical dosage unit manufacturing process control apparatus that includes means for acquiring a plurality of multi-pixel images of a flow of pharmaceutical dosage units at different wavelengths along an axis that is perpendicular to a direction of the flow of pharmaceutical dosage units, and means for processing the images acquired by the means for acquiring.

In a further general aspect, the invention features a pharmaceutical dosage unit manufacturing process control method including acquiring a plurality of multi-pixel images of a flow of pharmaceutical dosage units at different wavelengths along an axis that is perpendicular to a direction of the flow of pharmaceutical dosage units, processing the images acquired in the step of acquiring, and providing an indication about the flow of pharmaceutical dosage units based on the step of processing.

In another general aspect, the invention features a pharmaceutical dosage unit manufacturing process control apparatus that includes means for acquiring a plurality of multi-pixel line images of a flow of pharmaceutical dosage units along an axis that is perpendicular to a direction of the flow of pharmaceutical dosage units, and means for processing the images acquired in the step of acquiring as they are received. In preferred embodiments, the means for

acquiring can be operative to acquire the multi-pixel line images at a rate that is independent of a rate of advance of the flow of pharmaceutical dosage units.

In a further general aspect, the invention features a pharmaceutical dosage unit manufacturing process control method that includes acquiring a plurality of multi-pixel line images of a flow of pharmaceutical dosage units along an axis that is perpendicular to a direction of the flow of pharmaceutical dosage units, processing the images acquired in the step of acquiring as they are received, and providing an indication about the flow of pharmaceutical dosage units based on the step of processing.

In preferred embodiments, the step of acquiring can be operative to acquire the multi-pixel line images at a rate that is independent of a rate of advance of the flow of pharmaceutical dosage units. The step of acquiring can take place through individual packaging cells for the dosage units.

In another general aspect, the invention features a process control apparatus that includes means for acquiring a spectral data set from a process flow, the spectral data set expressing the response of areas of a surface of the process flow to different wavelengths of radiation, and means for mapping the spectral data set to a color image including differently colored areas that correspond to different ones of the parts of the process flow having differing responses to the different wavelengths. In preferred embodiments, the apparatus further includes means for evaluating the differently colored areas, having an input responsive to the means for mapping and an output for providing information about the areas.

In a further general aspect, the invention features a process control method that includes acquiring a spectral data set from a process flow, the spectral data set expressing the response of areas of a surface of the process flow to different wavelengths of radiation, and mapping the spectral data set to a color image including differently colored areas that correspond to different ones of the parts of the process flow having differing responses to the different wavelengths.

In another general aspect, the invention features a process control apparatus that includes an image sensor including an array of detector elements located generally along an axis that is perpendicular to a direction of a process flow, a spectrally selective element located in an optical path between a radiation source, the flow of pharmaceutical dosage units, and the image sensor, and a spectral processor responsive to an output of the image sensor and having an output port, the spectral processor including a spectral comparison module operative to compare spectral signatures from a library of known spectral signatures with spectral information acquired from the image sensor.

In preferred embodiments, the processor can be operative to receive, identify, and store spectral signatures for newly detected defects reported by the spectral comparison module. The spectral comparison module can be operative to perform spectral comparisons between the spectral information acquired from the image sensor and spectral signatures for known defects. The spectral comparison module can be operative to perform spectral comparisons between the spectral information acquired from the image sensor and spectral signatures for known ingredients in a pharmaceutical composition of the dosage units.

In a further general aspect, the invention features a process control apparatus that includes means for acquiring a plurality of multi-pixel images of a process flow at different wavelengths along an axis that is perpendicular to a direction of the process flow, and means for comparing spectral signatures from a library of known spectral signatures with spectral information acquired in the step of acquiring.

In preferred embodiments, the means for comparing can be operative to receive, identify, and store spectral signatures for new defects detected by the means for comparing. The means for comparing can be operative to compare spectral signatures for known defects with the spectral information acquired in by the means for acquiring,

In another general aspect, the invention features a process control method that includes acquiring a plurality of multi-pixel images of a process flow at different wavelengths along an axis that is perpendicular to a direction of the process flow, comparing spectral signatures from a library of known spectral signatures, including a plurality of spectral signatures for known defects, with spectral information acquired in the step of acquiring, and providing an indication about the flow of pharmaceutical dosage units based on the step of processing.

In preferred embodiments, the method further includes the steps of automatically identifying and storing spectral signatures for new defects detected in the step of comparing. The step of comparing can be operative to compare spectral signatures for known defects with the spectral information acquired in the step of acquiring,

In a further general aspect, the invention features a quality control apparatus for a pharmaceutical composition that includes a two-dimensional array sensor including a two-dimensional array of detector elements, a spectrally selective element located in an optical path between a radiation source, the flow of pharmaceutical dosage units, and the two-dimensional array sensor, and a spectral processor responsive to an output of the array sensor and having an output port. The spectral processor includes a mapping module operative to map spectral information into an image including different areas corresponding to different components of the pharmaceutical composition having differing responses to different wavelengths.

In preferred embodiments, the spectral processor can include a spectral comparison module operative to compare one or more known spectral signatures with spectral information acquired from the array sensor. The spectral comparison module can be operative to perform spectral comparisons between the spectral information acquired from the array sensor and spectral signatures for at least one known ingredient in the pharmaceutical composition. The spectral comparison module can be operative to perform spectral comparisons between the spectral information acquired from the array sensor and spectral signatures for a plurality of known ingredients in the pharmaceutical composition. The spectral processor can include a spectral comparison module operative to compare spectral information received by the array sensor from a reference sample with spectral information received by the array sensor. The spectrally selective element can include a diffraction grating. The apparatus can further include an image processor responsive to the output port of the spectral processor and operative to evaluate information from the spectral processor. The array sensor can be an infrared image sensor. The array sensor can be a near infrared image sensor. The radiation source can be directed at the pharmaceutical composition at a position to which the array sensor is responsive. The radiation source can be an infrared radiation source. The spectral processor can be operative to perform spectral manipulations on a spectral data set that includes image values at different wavelengths for each of a plurality of pixels corresponding to ones of the detector elements in the detector array. The quality control apparatus can be part of an on-line monitoring apparatus that continuously monitors a moving process web. The quality control apparatus can be operative to detect product defects that include non-uniformity of a size of capsules transported by the web. The quality control apparatus can be operative to detect product defects that include contamination or damage. The quality control apparatus can be operative to detect product defects that include product non-uniformity. The mapping module can be a color mapping module. The apparatus can further include an additional processor operative to evaluate the different areas, with the additional processor having an input responsive to the mapping module and an output for providing information about the areas. The spectral processor can be operative to perform univariate spectral manipulations on a spectral data set acquired from the array sensor. The spectral processor can be operative to perform multivariate spectral manipulations on a spectral data set acquired from the array sensor. The spectrally selective element can include a system that simultaneously projects a plurality of spectrally-discrete versions of a same image onto the array sensor.

In another general aspect, the invention features a quality control apparatus for a pharmaceutical composition that includes means for acquiring a two-dimensional spectral data

set expressing the response of areas of a surface to different wavelengths of radiation, and means for mapping the spectral data set to an image including different areas that correspond to different components of the pharmaceutical composition having differing responses to different wavelengths.

In preferred embodiments, the means for acquiring can include means for selecting spectral components of radiation received from ingredients of the pharmaceutical composition. The means for processing can include means for comparing spectral signatures from a library of known spectral signatures with spectral information acquired in the step of acquiring.

In a further general aspect, the invention features a quality control method for a pharmaceutical composition that includes acquiring a spectral data set expressing the response of areas of a surface to different wavelengths of radiation, and mapping the spectral data set to a color image including differently colored areas that correspond to different ones of the parts of surface having differing responses to the different wavelengths. In preferred embodiments, the method can further include the step of comparing spectral signatures from a library of known spectral signatures including signatures for one or more components of the pharmaceutical composition.

In another general aspect, the invention features a pharmaceutical dosage unit manufacturing process control apparatus that includes an image sensor including an array of detector elements located generally proximate a flow of pharmaceutical dosage units. A spectrally selective element simultaneously projects a plurality of spectrally-discrete versions of a same image of the flow of pharmaceutical dosage units onto the image sensor. A spectral processor is responsive to an output of the array sensor and having an output port.

In preferred embodiments, the spectrally selective element can be a filter having filter characteristics that vary along the direction of flow of pharmaceutical dosage units. The spectrally selective element can be a continuously gradeable filter. The spectral processor can include a color mapping module operative to map spectral information into a color image including differently colored areas that correspond to different parts of the flow of pharmaceutical dosage units having differing responses to different wavelengths. An additional processor can be operative to evaluate the differently colored areas, with the additional processor having an input responsive to the mapping module and an output for providing information about the areas. The mapping module can be operative to shift a plurality of the wavelengths in a similar manner. The spectral processor can include a spectral comparison module operative to compare spectral signatures from a library of known spectral signatures with spectral information acquired from the image sensor. The spectral comparison module can be operative to perform

spectral comparisons between the spectral information acquired from the image sensor and spectral signatures for known ingredients in a pharmaceutical composition of the dosage units. The processor can be operative to receive, identify, and store newly detected spectral signatures reported by the spectral comparison module. The library of known spectral signatures can include a plurality of spectral signatures for known defects. The processor can be operative to receive, identify, and store spectral signatures for newly detected defects reported by the spectral comparison module. The spectral processor can include a spectral comparison module operative to compare spectral information received by the image sensor from a reference sample located proximate the flow of pharmaceutical dosage units with spectral information received by the image sensor from the flow of pharmaceutical dosage units. The image sensor can be a two-dimensional array sensor that further includes detectors located generally along an axis that is parallel to the direction of the flow of pharmaceutical dosage units. The spectrally selective element can include a diffraction grating. The spectral processor can include a color mapping module operative to map spectral information into a color image including differently colored areas that correspond to different parts of the flow of pharmaceutical dosage units having differing responses to different wavelengths. The apparatus can further include an image processor responsive to the output port of the spectral processor and operative to evaluate information from the spectral processor. The image sensor can be an infrared image sensor. The image sensor can be a near infrared image sensor. The apparatus can further include a radiation source directed at the flow of pharmaceutical dosage units at a position to which the array sensor is responsive. The radiation source can be an infrared radiation source. The flow of pharmaceutical dosage units can include a series of dosage units located in rows generally perpendicular to the direction of the flow of pharmaceutical dosage units and wherein the image sensor includes, for each of the dosage units in a row, a plurality of detectors along the axis that is perpendicular to the direction of the flow of pharmaceutical dosage units. The spectral processor can be a real-time processor operative to process the images at a rate that is at least equal to a rate at which images are acquired by the image sensor. The spectral processor can be operative to sequentially process spectral data for each line image acquired by the image sensor. The spectral processor can be operative to receive image data from the image sensor at a rate that is independent of a rate of advance of the flow of pharmaceutical dosage units. The spectral processor can be operative to receive image data from the image sensor at a rate that is independent of a rate of advance of the flow of pharmaceutical dosage units. The spectral processor can be operative to perform univariate spectral manipulations on a spectral data set

acquired from the image sensor. The spectral processor can be operative to perform multivariate spectral manipulations on a spectral data set acquired from the image sensor.

In another general aspect, the invention features a pharmaceutical dosage unit manufacturing process control apparatus that includes means for simultaneously projecting a plurality of spectrally-discrete versions of a same image of a flow of pharmaceutical dosage units onto an image sensor, and means for processing the images acquired by the means for acquiring. In preferred embodiments, the means for simultaneously projecting can include a filter having filter characteristics that vary along the direction of flow of pharmaceutical dosage units.

In a further general aspect, the invention features a pharmaceutical dosage unit manufacturing process control method that includes simultaneously projecting a plurality of spectrally-discrete versions of a same image of a flow of pharmaceutical dosage units onto an image sensor, acquiring a plurality of multi-pixel images of the flow of pharmaceutical dosage units, processing the images acquired in the step of acquiring, and providing an indication about the flow of pharmaceutical dosage units based on the step of processing. In preferred embodiments, the step of simultaneously projecting can include a step of filtering.

Systems according to the invention are advantageous in that they can continuously test the actual composition of each dosage unit within its packaging. Such systems can therefore screen for errors in coloring of ingredients, for contamination or breakdown that occurs independent of coloring, and for other types of errors that might not otherwise be detected. And because systems according to the invention can perform their composition measurements through the end-user package walls, they can detect contamination or damage that occurs during packaging.

Performing composition analysis by comparing spectral information with libraries of known spectral signatures, allows small concentrations of potentially dangerous contaminants, such as potent toxins, to be detected. Without being correlated to a specific spectral signature, such small concentrations might have little effect on prior art process monitoring methods, and might therefore be dismissed as within an error margin.

Performing composition analysis by comparing spectral information with libraries of known spectral signatures may also allow for the detection of unexpected components. Comparing acquired spectral information with libraries of components may uncover contaminants not normally associated with the process. This may allow a manufacturer to avert hazards that arise out of unforseen circumstances, such as supplier errors or deliberate tampering.

Performing composition analysis by comparing spectral information with libraries of known spectral signatures may further allow for the detection of subtle shifts in the process.

Because relative quantities of ingredients can be directly measured, a change in the ratio of these ingredients can be detected. While such changes may not warrant rejection of the products, they may allow the process to be optimized and prevent the process from drifting out of its intending operating range.

Systems according to the invention may also be advantageous in that they can allow a process engineer to select optimal process variables to monitor. By mapping selected spectral information into an image, which is then processed by an image processor, systems according to the invention can apply the image processing resources to the spectral data that correlates best to known and predicted failure modes. And because the system acquires information about a large number of wavelengths simultaneously, a system operator can try a number of different approaches to achieve the best results.

Brief Description of the Drawings

Fig. 1 is a diagram of an embodiment of a pharmaceutical dosage unit manufacturing process control system according to the invention, including a perspective portion illustrating the relationship between the image sensor, the spectrally selective element, and the process stream;

Fig. 2 is a plan view diagram of an image sensor for use with the process control system of Fig. 1;

Fig. 3 is a plan view diagram illustrating output of the system of Fig. 1;

Fig. 4 is a flowchart illustrating the operation of the embodiment of Fig. 1; and

Fig. 5 is a diagram of a second embodiment of a pharmaceutical dosage unit manufacturing process control system according to the invention, including a perspective portion illustrating the relationship between the image sensor, the spectrally selective element, and the process stream.

In the figures, like reference numbers represent like elements.

Description of an Illustrative Embodiment

Referring to Fig. 1, a pharmaceutical dosage unit manufacturing process control system according to the invention features an image sensor 10 and a spectrally selective element 12 facing a web 16 that carries a series of parallel rows of pharmaceutical dosage units 18, such as capsules, tablets, pellets, ampoules, or vials, in a process flow direction. For example, the web can carry a continuous stream of blister-packaged tablets from the output of a packaging machine. The image sensor is a multi-element sensor that includes at least a series of adjacent sensing elements located generally along an axis that is perpendicular to the flow direction. The

spectrally selective element is a wavelength separating element, and is preferably a dispersive element, such as a diffraction grating or a prism-based monochromator.

Referring to Figs. 1-2, the image sensor 10 is preferably a two-dimensional array sensor that includes a two-dimensional array of detector elements made up of a series of lines of elements (A1 - An, B1 - Bn, ... N1 – Nn) that are each located generally along an axis that is perpendicular to the flow direction. The image sensor can include an array of integrated semiconductor elements, such as a Charge-Coupled Device (CCD) array, and is preferably sensitive to infrared radiation. Uncooled Idium-Galium-Arsenide (InGaAs) arrays, which are sensitive to near infrared wavelengths, are suitable image sensors, although sensitivity to longer wavelengths would be desirable. It is contemplated that the sensors should preferably have dimensions of at least 64 x 64 or even 256 x 256. Where such sensors are not square, they should be oriented with their longer dimension in the direction of the process flow, as spectral information appears to be typically more important than spatial information given the nature of pharmaceutical mass-production equipment.

The system also includes an image acquisition interface 22 having an input port responsive to an output port of the image sensor 10. The image acquisition interface receives and/or formats image signals from the image sensor. It can include an off-the shelf frame buffer card with a 12-16 bit dynamic range, such as are available from Matrox Electronic Systems Ltd. of Montreal, Canada, and Dipix Technologies, of Ottawa, Canada.

A spectral processor 26 has an input responsive to the image acquisition interface 22. This spectral processor has a control output provided to a source control interface 20, which can power and control an illumination source 14. The illumination source for near infrared measurements is preferably a Quartz-Tungsten-Halide lamp.

The spectral processor 26 is also operatively connected to a standard input/output (IO) interface 30 and to a local spectral library 24. The local spectral library includes locally-stored spectral signatures for known process components. These components can include ingredients, process products, or results of process defects or contamination. The IO interface can also operatively connect the spectral processor to a remote spectral library 28.

The spectral processor 26 is operatively connected to an image processor 32 as well. The image processor can be an off-the-shelf programmable industrial image processor, that includes special-purpose image processing hardware and image evaluation routines that are operative to evaluate shapes and colors of manufactured objects in industrial environments. Such systems are available from, for example, Cognex, Inc.

In one embodiment, the system is based on the so-called IBM-PC architecture. The image acquisition interface 22, IO interface 30, and image processor 32 each occupy expansion slots on the system bus. The spectral processor is implemented using special-purpose spectral processing routines loaded on the host processor, and the local spectral library is stored in local mass storage, such as disk storage. Of course, other structures can be used to implement systems according to the invention, including various combinations of dedicated hardware and special-purpose software running on general-purpose hardware. In addition, the various elements and steps described can be reorganized, divided, and combined in different ways without departing from the scope and spirit of the invention. For example, many of the separate operations described above can be performed simultaneously according to well-known pipelining and parallel processing principles.

In operation, referring to Figs. 1-4, the spectrally selective element 12 is sensitive to the radiation reflected off of a line across the process web 16, and collimated by a first-stage optic, such as a lens (not shown). The spectrally selective element separates the spectral components of the reflected radiation along the axis of the process flow. As a result, the successive lines A1 - An, B1 - Bn, ... N1 - Nn of the image sensor are exposed to spectral components of the radiation that are of successively higher or lower wavelengths, depending on the relative orientation of the spectrally selective element and the image sensor. In one embodiment, a portion of the line image extends beyond the web to overlap with a stationary reference sample 19 located adjacent the web. This implementation can allow for the removal of transfer of calibration requirements between systems that collect pure component spectra for spectral comparison.

At a predetermined repetition rate, the image acquisition interface 22 acquires a data set representative of the radiation incident on the image sensor (i.e., a spectral line image—step 40). This data set includes image values for each of the pixels along the imaged line on the process web at a number of different wavelengths. In the case of a 256 x 256 array, intensity values at 256 different wavelengths will be stored for each of 256 points on the imaged line. Once it has been acquired, the image acquisition interface transfers this data set to the spectral processor 26.

The spectral processor 26 then evaluates the acquired spectral line image (step 42). This evaluation can include a variety of univariate and multivariate spectral manipulations. These can include comparing received spectral information with spectral signatures stored in the library, comparing received spectral information attributable to manufactured dosage units with information attributable to the reference sample, or evaluating simplified test functions, such as looking for the absence of a particular wavelength or combination of wavelengths. Multivariate spectral manipulations are discussed in more detail in "Multivariate Image Analysis," by Paul

Geladi and Hans, Grahn, available from John Wiley, ISBN No. 0-471-93001-6, which is herein incorporated by reference.

As a result of its evaluation, the spectral processor 26 may detect known components (step 44) and/or unknown components (step 46). If an unknown component is detected, the system records a spectral signature entry for the new component type in the local spectral library 24 (step 48). The system can also attempt to identify the newly detected component in an extended or remote library 28, such as by accessing it through a telephone line or computer network (step 50). The system then flags the detection of the new component to the system operator, and reports any retrieved candidate identities (step 52).

Once component identification is complete, the system maps the different detected components into a color (such as grayscale) line image (step 54). As the system processes further spectral line images, it accumulates a two-dimensional colored image frame. When complete, this image can be transferred to the image processor (step 58), which evaluates the shape and color of the dosage units (step 60), issues rejection signals for rejected dosage units, and compiles operation logs.

As shown in Fig. 3, the color image will resemble the process web, although it may be stretched or squeezed in the direction of the process flow, depending on the acquisition rate. The image can include a color that represents the composition of the web 16. It will can also include colors that represent known good components 18A, colors that represent known defect components 18B, and colors that represent unknown components 18C. The mapping can also take the form of a spectral shift, in which some or all of the acquired spectral components are shifted in a similar manner, preserving the relationship between wavelengths. Note that because the image maps components to colors, it provides information about spatial distribution of the pharmaceutical composition in addition to identifying its components.

While the system can operate in real-time to detect defective products, its results can also be analyzed further off-line. For example, some or all of the spectral data sets, or running averages derived from these data sets can be stored and periodically compared with extensive off-line databases of spectral signatures to detect possible new contaminants. Relative spectral intensities arising from relative amounts of reagents or ingredients can also be computed to determine if the process is optimally adjusted.

Note that the system presented above is self-scanning. Although it can be synchronized with the process by a sensor, such synchronization is not required. The system can therefore be easily retrofit to existing installations and does not require any moving parts.

The acquisition method employed by the process control system can also be computationally efficient. Since data is acquired and spectrally processed on a line-by-line basis, the spectral processor does not have to store large amounts of intermediate results. Once a line has been mapped to a colored line image, all of the acquired data and intermediate results can be discarded, and a new line processed. This can allow the system to operate in real time with relatively simple computer components, keeping the overall system cost low.

Referring to Fig. 5, a second embodiment of a pharmaceutical dosage unit manufacturing process control system according to the invention includes a variable-bandpass filter 12a between the two-dimensional array sensor and the process stream. This filter has a narrow pass-band with a center wavelength that varies along the process direction. The leading edge A of the filter passes shorter wavelengths, and as the distance from the leading edge along the process flow direction increases, the filter passes successively longer wavelengths. At the trailing edge N of the filter, the filter passes a narrow range of the longest wavelengths. The orientation of the filter can also be reversed, so that the pass-band center wavelength decreases along the process flow direction. Although the filter has been illustrated as a series of strips located perpendicular to the process flow direction, it can be manufactured in practice by continuously varying the dielectric thickness in an interference filter. Preferably, the filter should have a range of pass-bands that matches the range of the camera. Suitable filters are available, for example, from Optical Coatings Laboratory, Inc. of Santa Rosa, California.

In operation of this embodiment, acquisition interface 22 acquires data representing a series of variably-filtered, two-dimensional images. These two-dimensional images each include image values for the pixels in a series of adjacent lines perpendicular to the process web. Because of the action of the variable-bandpass filter, the detected line images that make up each two-dimensional image will have a spectral content that varies along the process direction.

The variably filtered images are combined as they are acquired in order to obtain full-range spectral images. As each imaged line progresses along the web, each successive line (N1 ... A1) of elements in the array sensor 10 will sense radiation that has been filtered through a corresponding line (N ... A) of the filter. These individual line images can be assembled to create a full-spectrum line image. The assembly can take place by itself, or in combination with other operations, such as digital filtering operations. This embodiment is particularly advantageous because the variable-bandpass filter is relatively inexpensive and robust.

Another approach involves the use of an optical system that simultaneously projects a number of spectrally-discrete versions of the same two-dimensional image onto the array sensor 10. Such systems are described in PCT application No. PCT/US98/14218 published under No.

WO09902950, which are herein incorporated by reference. The use of these systems is advantageous in that they allow high data throughputs for a given web speed, without adding moving parts. Systems of this type are available from Optical Insights, Inc of Tucson, Arizona.

A further embodiment employs multi-source arrays to provide successive illumination at different wavelengths and thereby obtain spectral information from the process. Such arrays are described in a copending provisional application entitled "Multi-Source Arrays," filed on the same day as this application, and herein incorporated by reference.

The present invention has now been described in connection with a number of specific embodiments thereof. However, numerous modifications which are contemplated as falling within the scope of the present invention should now be apparent to those skilled in the art. For example, aspects of the invention may also be applicable to other types of manufacturing processes, such in detecting the presence of undesirable by-products in the manufacture of plastic articles. In addition, while a two-dimensional image sensor with a dispersive or graded spectrally selective element is at present contemplated to be the best approach to acquiring line image data, a one-dimensional image sensor coupled with a high-speed filtering system might allow a suitable amount of data to be acquired in some circumstances. Therefore, it is intended that the scope of the present invention be limited only by the scope of the claims appended hereto. In addition, the order of presentation of the claims should not be construed to limit the scope of any particular term in the claims.

What is claimed is:

CLAIMS

1. A pharmaceutical dosage unit manufacturing process control apparatus, comprising:

an image sensor including an array of detector elements located generally along an axis that is perpendicular to a direction of a flow of pharmaceutical dosage units,

a spectrally selective element located in an optical path between a radiation source, the flow of pharmaceutical dosage units, and the image sensor, and

a spectral processor responsive to an output of the image sensor and having an output port.

2. The apparatus of claim 1 wherein the spectral processor includes a color mapping module operative to map spectral information into a color image including differently colored areas that correspond to different parts of the flow of pharmaceutical dosage units having differing responses to different wavelengths.

3. The apparatus of claim 2 further including an additional processor operative to evaluate the differently colored areas, the additional processor having an input responsive to the mapping module and an output for providing information about the areas.

4. The apparatus of claim 2 wherein the mapping module is operative to shift a plurality of the wavelengths in a similar manner.

5. The apparatus of claim 1 wherein the spectral processor includes a spectral comparison module operative to compare spectral signatures from a library of known spectral signatures with spectral information acquired from the image sensor.

6. The apparatus of claim 5 wherein the spectral comparison module is operative to perform spectral comparisons between the spectral information acquired from the image sensor and spectral signatures for known ingredients in a pharmaceutical composition of the dosage units.

7. The apparatus of claim 5 wherein the processor is operative to receive, identify, and store newly detected spectral signatures reported by the spectral comparison module.

8. The apparatus of claim 5 wherein the library of known spectral signatures includes a plurality of spectral signatures for known defects.

9. The apparatus of claim 8 wherein the processor is operative to receive, identify, and store spectral signatures for newly detected defects reported by the spectral comparison module.

10. The apparatus of claim 1 wherein the spectral processor includes a spectral comparison module operative to compare spectral information received by the image sensor from a reference sample located proximate the flow of pharmaceutical dosage units with spectral information received by the image sensor from the flow of pharmaceutical dosage units.

11. The apparatus of claim 1 wherein the image sensor is a two-dimensional array sensor that further includes detectors located generally along an axis that is parallel to the direction of the flow of pharmaceutical dosage units.

12. The apparatus of claim 11 wherein the spectrally selective element includes a diffraction grating.

13. The apparatus of claim 11 wherein the spectral processor includes a color mapping module operative to map spectral information into a color image including differently colored areas that correspond to different parts of the flow of pharmaceutical dosage units having differing responses to different wavelengths.

14. The apparatus of claim 1 further including an image processor responsive to the output port of the spectral processor and operative to evaluate information from the spectral processor.

15. The apparatus of claim 1 wherein the image sensor is an infrared image sensor.

16. The apparatus of claim 1 wherein the image sensor is a near infrared image sensor.

17. The apparatus of claim 1 further including the radiation source directed at the flow of pharmaceutical dosage units at a position to which the image sensor is responsive.

18. The apparatus of claim 17 wherein the radiation source is an infrared radiation source.

19. The apparatus of claim 1 wherein the flow of pharmaceutical dosage units includes a series of dosage units located in rows generally perpendicular to the direction of the flow of pharmaceutical dosage units and wherein the image sensor includes, for each of the dosage units in a row, a plurality of detectors along the axis that is perpendicular to the direction of the flow of pharmaceutical dosage units.

20. The apparatus of claim 1 wherein the spectral processor is a real-time processor operative to process the images at a rate that is at least equal to a rate at which images are acquired by the image sensor.

21. The apparatus of claim 20 wherein the spectral processor is operative to sequentially process spectral data for each line image acquired by the image sensor.

22. The apparatus of claim 21 wherein the spectral processor is operative to receive image data from the image sensor at a rate that is independent of a rate of advance of the flow of pharmaceutical dosage units.

23. The apparatus of claim 1 wherein the spectral processor is operative to receive image data from the image sensor at a rate that is independent of a rate of advance of the flow of pharmaceutical dosage units.

24. The apparatus of claim 1 wherein the spectral processor is operative to perform univariate spectral manipulations on a spectral data set acquired from the image sensor.

25. The apparatus of claim 1 wherein the spectral processor is operative to perform multivariate spectral manipulations on a spectral data set acquired from the image sensor.

26. The apparatus of claim 1 wherein the spectrally selective element is a filter having filter characteristics that vary along the direction of flow of pharmaceutical dosage units.

27. The apparatus of claim 26 wherein the spectrally selective element is a continuously gradeable filter.

28. The apparatus of claim 1 wherein the spectrally selective element includes a system that simultaneously projects a plurality of spectrally-discrete versions of a same image onto the image sensor.

29. A pharmaceutical dosage unit manufacturing process control apparatus, comprising:

means for acquiring a plurality of multi-pixel images of a flow of pharmaceutical dosage units at different wavelengths along an axis that is perpendicular to a direction of the flow of pharmaceutical dosage units, and

means for processing the images acquired by the means for acquiring.

30. A pharmaceutical dosage unit manufacturing process control method, comprising:

acquiring a plurality of multi-pixel images of a flow of pharmaceutical dosage units at different wavelengths along an axis that is perpendicular to a direction of the flow of pharmaceutical dosage units,

processing the images acquired in the step of acquiring, and

providing an indication about the flow of pharmaceutical dosage units based on the step of processing.

31. A pharmaceutical dosage unit manufacturing process control apparatus, comprising:

means for acquiring a plurality of multi-pixel line images of a flow of pharmaceutical dosage units along an axis that is perpendicular to a direction of the flow of pharmaceutical dosage units, and

means for processing the images acquired in the step of acquiring as they are received.

32. The apparatus of claim 31 wherein the means for acquiring is operative to acquire the multi-pixel line images at a rate that is independent of a rate of advance of the flow of pharmaceutical dosage units.

33. A pharmaceutical dosage unit manufacturing process control method, comprising:

acquiring a plurality of multi-pixel line images of a flow of pharmaceutical dosage units along an axis that is perpendicular to a direction of the flow of pharmaceutical dosage units,

processing the images acquired in the step of acquiring as they are received, and

providing an indication about the flow of pharmaceutical dosage units based on the step of processing.

34. The method of claim 33 wherein the step of acquiring is operative to acquire the multi-pixel line images at a rate that is independent of a rate of advance of the flow of pharmaceutical dosage units.

35. The method of claim 33 wherein the step of acquiring takes place through individual packaging cells for the dosage units.

36. A process control apparatus, comprising:

means for acquiring a spectral data set from a process flow, the spectral data set expressing the response of areas of a surface of the process flow to different wavelengths of radiation, and

means for mapping the spectral data set to a color image including differently colored areas that correspond to different ones of the parts of the process flow having differing responses to the different wavelengths.

37. The apparatus of claim 36 further including means for evaluating the differently colored areas, having an input responsive to the means for mapping and an output for providing information about the areas.

38. A process control method, comprising:

acquiring a spectral data set from a process flow, the spectral data set expressing the response of areas of a surface of the process flow to different wavelengths of radiation, and

mapping the spectral data set to a color image including differently colored areas that correspond to different ones of the parts of the process flow having differing responses to the different wavelengths.

39. A process control apparatus, comprising:

an image sensor including an array of detector elements located generally along an axis that is perpendicular to a direction of a process flow,

a spectrally selective element located in an optical path between a radiation source, the flow of pharmaceutical dosage units, and the image sensor, and

a spectral processor responsive to an output of the image sensor and having an output port, the spectral processor including a spectral comparison module operative to compare spectral signatures from a library of known spectral signatures with spectral information acquired from the image sensor.

40. The apparatus of claim 39 wherein the processor is operative to receive, identify, and store spectral signatures for newly detected defects reported by the spectral comparison module.

41. The apparatus of claim 39 wherein the spectral comparison module is operative to perform spectral comparisons between the spectral information acquired from the image sensor and spectral signatures for known defects.

42. The apparatus of claim 39 wherein the spectral comparison module is operative to perform spectral comparisons between the spectral information acquired from the image sensor and spectral signatures for known ingredients in a pharmaceutical composition of the dosage units.

43. A process control apparatus, comprising:

means for acquiring a plurality of multi-pixel images of a process flow at different wavelengths along an axis that is perpendicular to a direction of the process flow, and

means for comparing spectral signatures from a library of known spectral signatures with spectral information acquired in the step of acquiring.

44. The apparatus of claim 43 wherein the means for comparing is operative to receive, identify, and store spectral signatures for new defects detected by the means for comparing.

45. The apparatus of claim 43 wherein the means for comparing is operative to compare spectral signatures for known defects with the spectral information acquired in by the means for acquiring,

46. A process control method, comprising:

acquiring a plurality of multi-pixel images of a process flow at different wavelengths along an axis that is perpendicular to a direction of the process flow,

comparing spectral signatures from a library of known spectral signatures, including a plurality of spectral signatures for known defects, with spectral information acquired in the step of acquiring, and

providing an indication about the flow of pharmaceutical dosage units based on the step of processing.

47. The method of claim 46 further including the steps of automatically identifying and storing spectral signatures for new defects detected in the step of comparing.

48. The apparatus of claim 46 wherein the step of comparing is operative to compare spectral signatures for known defects with the spectral information acquired in the step of acquiring,

49. A quality control apparatus for a pharmaceutical composition, comprising:

a two-dimensional array sensor including a two-dimensional array of detector elements,

a spectrally selective element located in an optical path between a radiation source, the flow of pharmaceutical dosage units, and the two-dimensional array sensor, and

a spectral processor responsive to an output of the array sensor and having an output port, wherein the spectral processor includes a mapping module operative to map spectral information into an image including different areas corresponding to different components of the pharmaceutical composition having differing responses to different wavelengths.

50. The apparatus of claim 49 wherein the spectral processor includes a spectral comparison module operative to compare one or more known spectral signatures with spectral information acquired from the array sensor.

51. The apparatus of claim 50 wherein the spectral comparison module is operative to perform spectral comparisons between the spectral information acquired from the array sensor and spectral signatures for at least one known ingredient in the pharmaceutical composition.

52. The apparatus of claim 50 wherein the spectral comparison module is operative to perform spectral comparisons between the spectral information acquired from the array sensor and spectral signatures for a plurality of known ingredients in the pharmaceutical composition.

53. The apparatus of claim 49 wherein the spectral processor includes a spectral comparison module operative to compare spectral information received by the array sensor from a reference sample with spectral information received by the array sensor.

54. The apparatus of claim 49 wherein the spectrally selective element includes a diffraction grating.

55. The apparatus of claim 49 further including an image processor responsive to the output port of the spectral processor and operative to evaluate information from the spectral processor.

56. The apparatus of claim 49 wherein the array sensor is an infrared image sensor.

57. The apparatus of claim 49 wherein the array sensor is a near infrared image sensor.

58. The apparatus of claim 49 further including the radiation source directed at the pharmaceutical composition at a position to which the array sensor is responsive.

59. The apparatus of claim 58 wherein the radiation source is an infrared radiation source..

60. The apparatus of claim 49 wherein the spectral processor is operative to perform spectral manipulations on a spectral data set that includes image values at different wavelengths for each of a plurality of pixels corresponding to ones of the detector elements in the detector array.

61. The apparatus of claim 49 wherein the quality control apparatus is part of an on-line monitoring apparatus that continuously monitors a moving process web.

62. The apparatus of claim 61 wherein the quality control apparatus is operative to detect product defects that include non-uniformity of a size of capsules transported by the web.

63. The apparatus of claim 49 wherein the quality control apparatus is operative to detect product defects that include contamination or damage.

64. The apparatus of claim 49 wherein the quality control apparatus is operative to detect product defects that include product non-uniformity.

65. The apparatus of claim 49 wherein the mapping module is a color mapping module.

66. The apparatus of claim 49 further including an additional processor operative to evaluate the different areas, the additional processor having an input responsive to the mapping module and an output for providing information about the areas.

67. The apparatus of claim 49 wherein the spectral processor is operative to perform univariate spectral manipulations on a spectral data set acquired from the array sensor.

68. The apparatus of claim 49 wherein the spectral processor is operative to perform multivariate spectral manipulations on a spectral data set acquired from the array sensor.

69. The apparatus of claim 49 wherein the spectrally selective element includes a system that simultaneously projects a plurality of spectrally-discrete versions of a same image onto the array sensor.

70. A quality control apparatus for a pharmaceutical composition, comprising:

means for acquiring a two-dimensional spectral data set expressing the response of areas of a surface to different wavelengths of radiation, and

means for mapping the spectral data set to an image including different areas that correspond to different components of the pharmaceutical composition having differing responses to different wavelengths.

71. The apparatus of claim 70 wherein the means for acquiring includes means for selecting spectral components of radiation received from ingredients of the pharmaceutical composition.

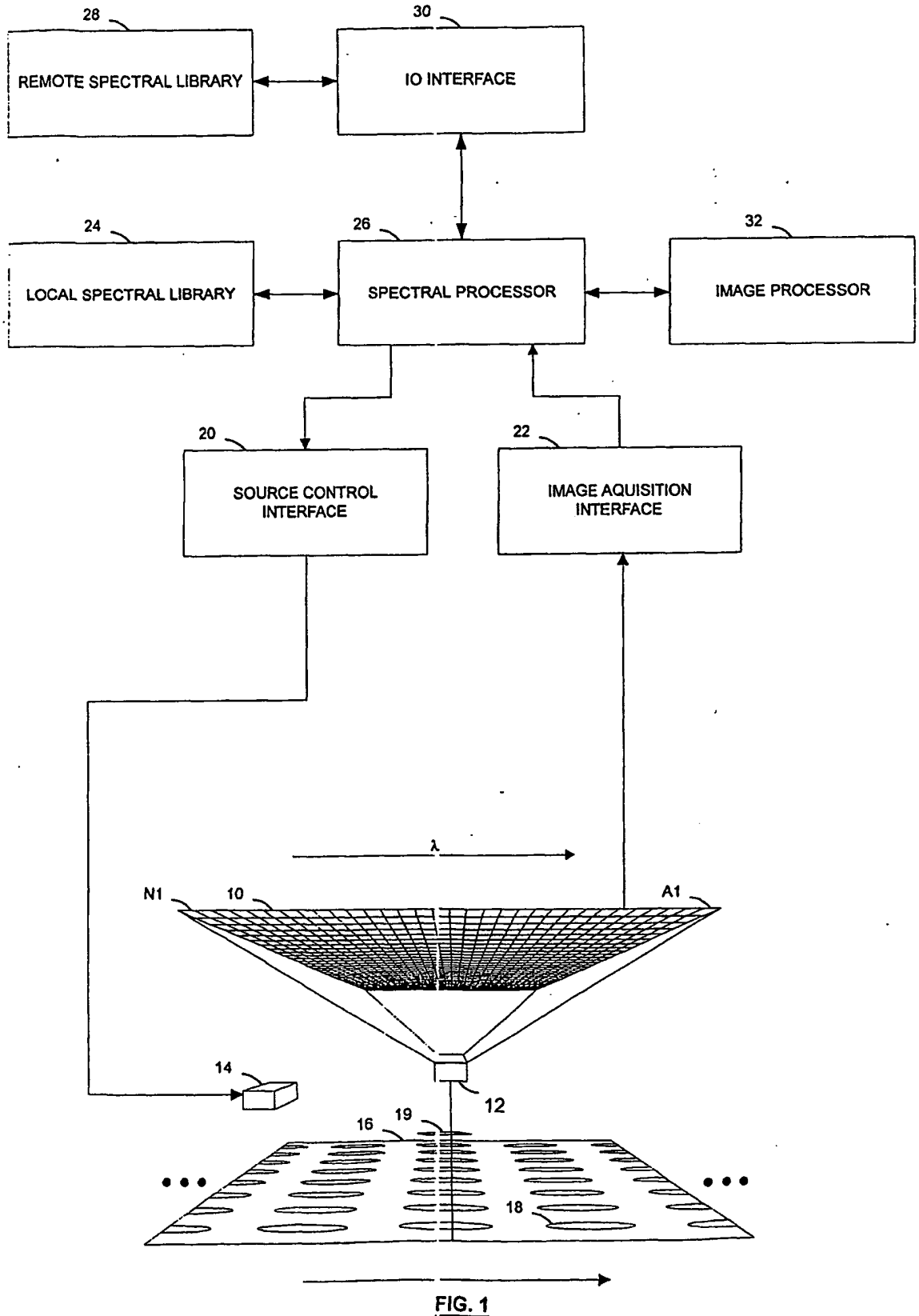
72. The apparatus of claim 70 wherein the means for processing includes means for comparing spectral signatures from a library of known spectral signatures with spectral information acquired in the step of acquiring.

73. A quality control method for a pharmaceutical composition, comprising:

acquiring a spectral data set expressing the response of areas of a surface to different wavelengths of radiation, and

mapping the spectral data set to a color image including differently colored areas that correspond to different ones of the parts of surface having differing responses to the different wavelengths.

74. The method of claim 73 further including the step of comparing spectral signatures from a library of known spectral signatures including signatures for one or more components of the pharmaceutical composition.


28
REMOTE SPECTRAL LIBRARY
30
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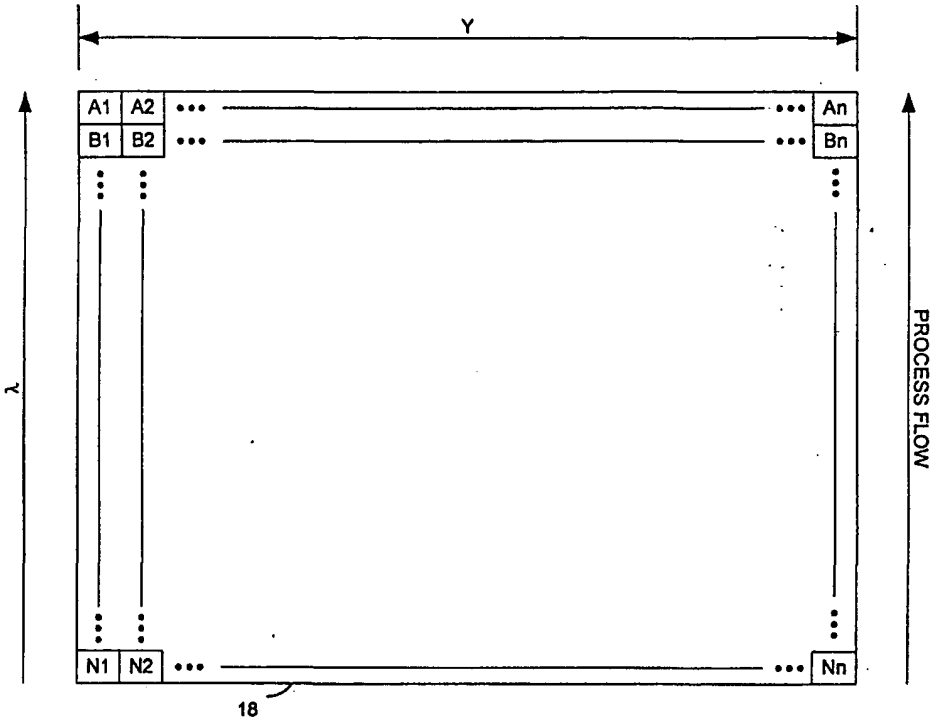
24
LOCAL SPECTRAL LIBRARY
26
SPECTRAL PROCESSOR
32
IMAGE PROCESSOR
20
SOURCE CONTROL INTERFACE
22
IMAGE AQUISITION INTERFACE
λ
N1
10
A1
14
12
16
19
18

FIG. 1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PROCESS FLOW

FIG. 2

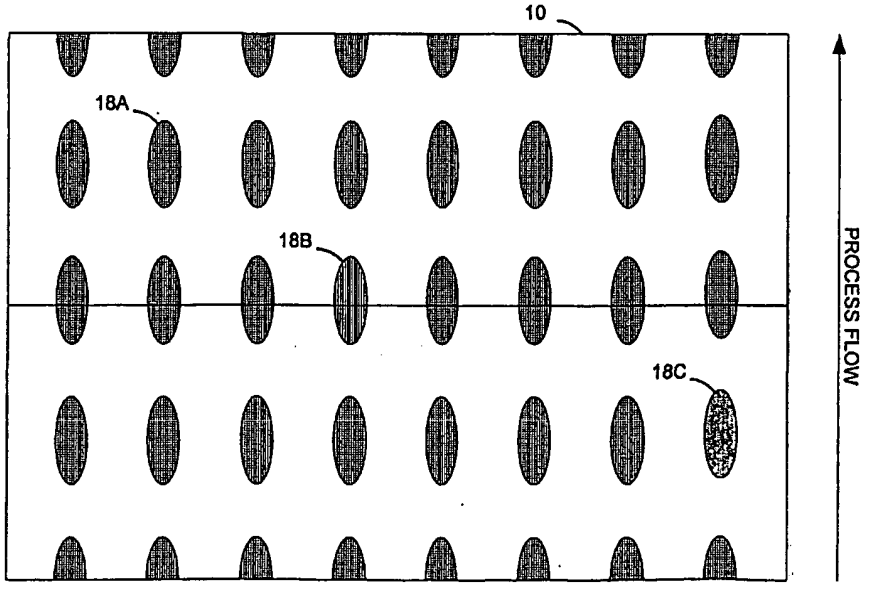

10
18A
18B
18C
PROCESS FLOW

FIG. 3

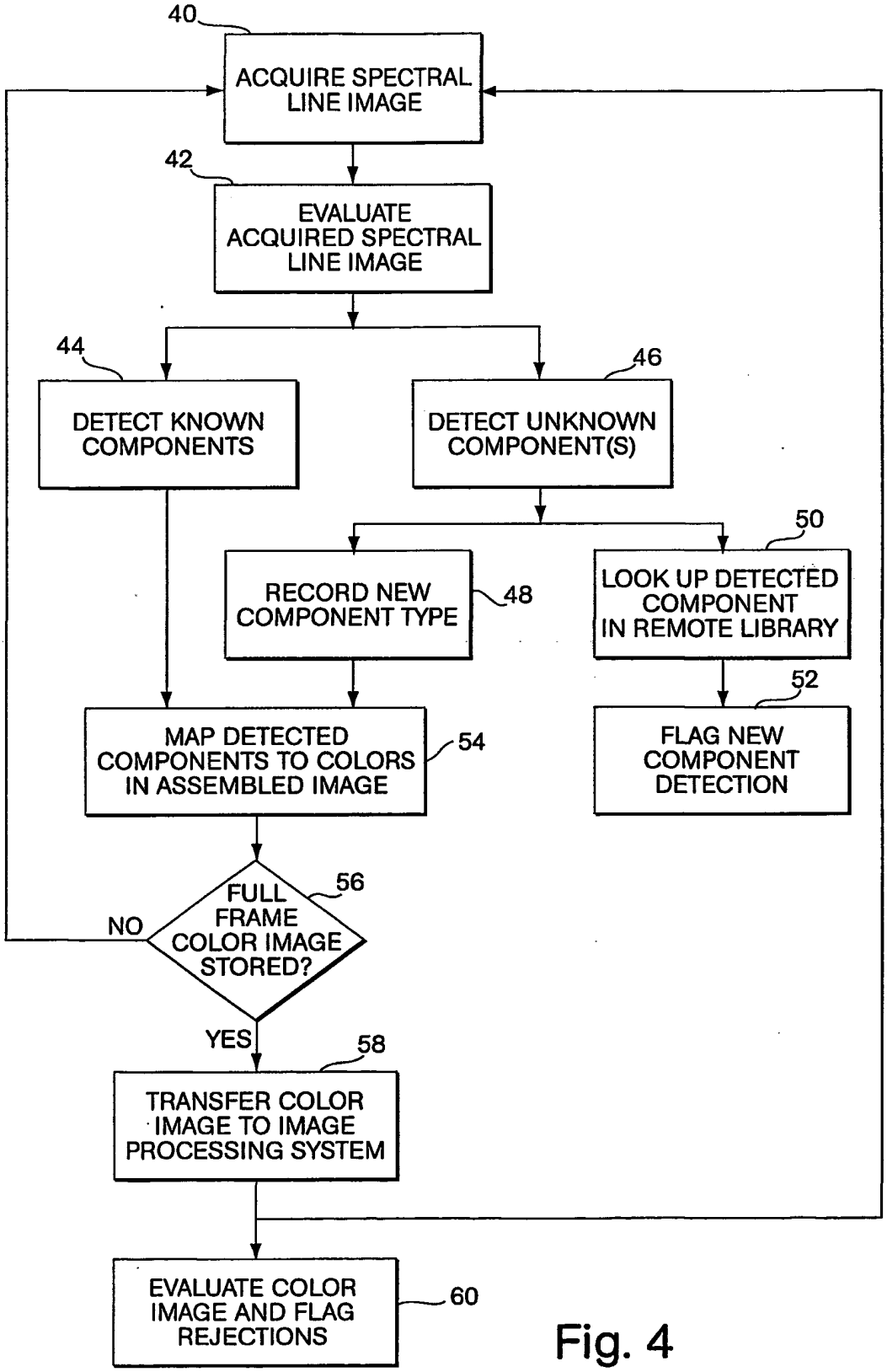
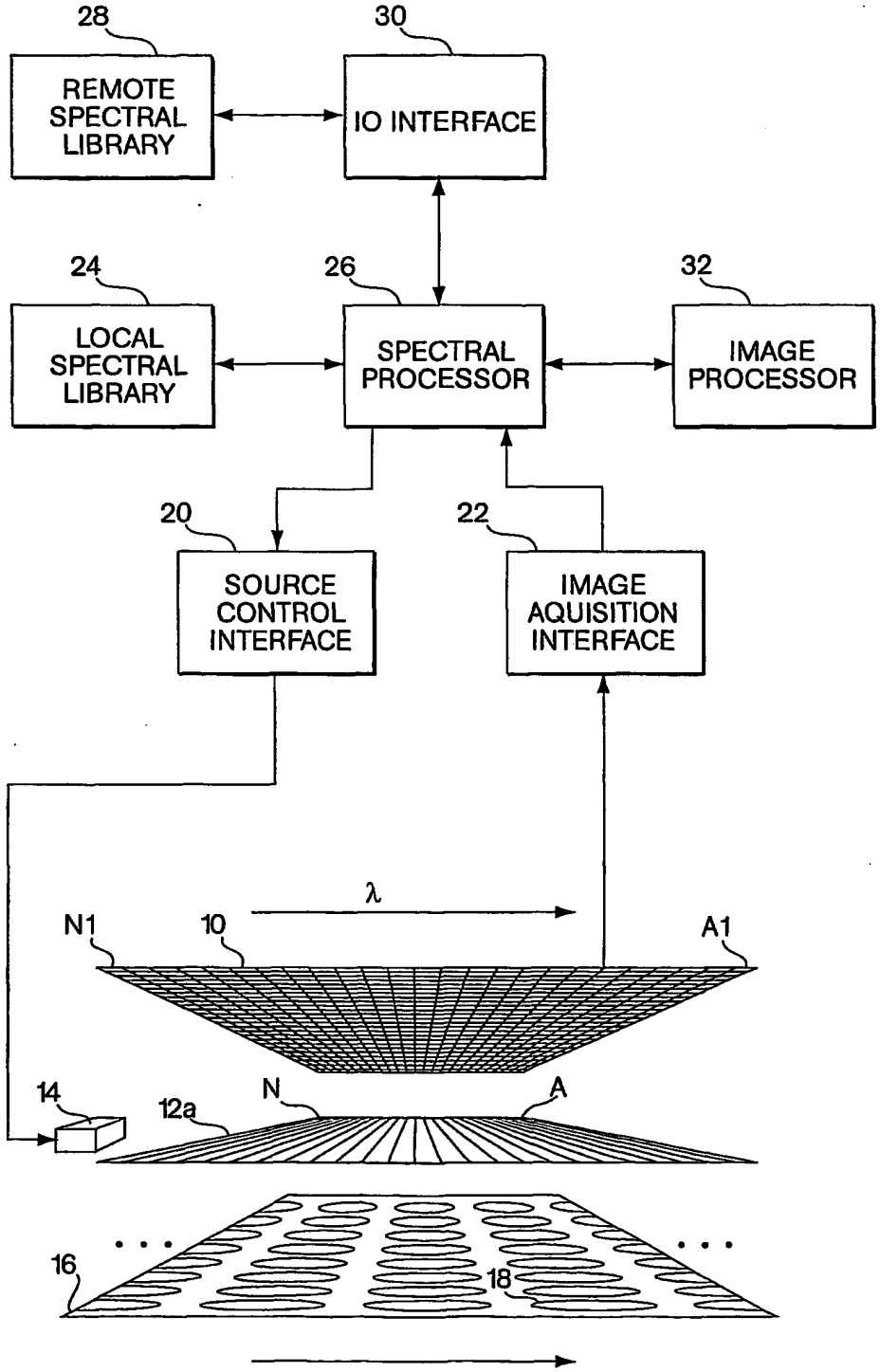

40
ACQUIRE SPECTRAL LINE IMAGE
42
EVALUATE ACQUIRED SPECTRAL LINE IMAGE
44
DETECT KNOWN COMPONENTS
46
DETECT UNKNOWN COMPONENT(S)
50
RECORD NEW COMPONENT TYPE
48
LOOK UP DETECTED COMPONENT IN REMOTE LIBRARY
52
MAP DETECTED COMPONENTS TO COLORS IN ASSEMBLED IMAGE
54
FLAG NEW COMPONENT DETECTION
56
FULL FRAME COLOR IMAGE STORED?
NO
YES
58
TRANSFER COLOR IMAGE TO IMAGE PROCESSING SYSTEM
EVALUATE COLOR IMAGE AND FLAG REJECTIONS
60

Fig. 4


28
REMOTE SPECTRAL LIBRARY
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LOCAL SPECTRAL LIBRARY
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SPECTRAL PROCESSOR
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IMAGE PROCESSOR
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SOURCE CONTROL INTERFACE
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IMAGE AQUISITION INTERFACE
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N1
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A1
14
12a
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A
16
18

Fig. 5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/19271

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) :G06K 9/00; B07C 5/342; G01J 5/02
US CL :382/165; 209/580; 250/339.12
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 382/165; 209/580; 250/339.12

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,615,009 A (SAKURA et al) 25 March 1997, ALL	1-75
A	US 5,558,231 A (WEIER) 24 September 1996, ALL	1-75
A	US 5,504,332 A (RICHMOND et al) 2 April 1996, ALL	1-75

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
30 DECEMBER 2000

Date of mailing of the international search report
22 MAR 2001

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230

Authorized officer
ISHRAT SHERALI
Telephone No. (703) 308-9556

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